P.E.T.Net® Pharmaceuticals, Inc.
Fueling the Power of P.E.T.

June 5, 2002

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

VIA Electronic Submission

RE: Docket No. 98D-0266
Draft Guidance on Current Good Manufacturing Practice for Positron Emission Tomography Drug Products; Availability [67 **Federal Register** 15404]

Dear Sir/Madam:

PETNet® Pharmaceuticals, Inc. (PETNet) is a nationwide health product company dedicated to positron emission tomography (PET). We operate 30 cyclotron-based PET nuclear pharmacies in more than twenty states, and we are the leading producer of radiopharmaceuticals for PET. We estimate that our MetaTrace® brand of F 18 Fludeoxyglucose (FDG) accounts for almost 60% of the commercially-supplied FDG in use today.

As such, PETNet is affected by the preliminary draft proposed rule, and we are interested in and well qualified to comment on these proposed regulations. PETNet has provided input on the development PET CGMP's for several years, including the Public Meeting held on May 21, 2002, ("Public Meeting") to discuss the preliminary draft proposed rule.

In general, PETNet supports the draft guidance document and is pleased to provide these comments in an effort to assist the further development of the guidance document.

The Draft Guidance Document

Comment

In general, we believe guidance documents can be a useful method for dissemination of acceptable embodiments of GMP regulations. We also believe that, as stated by FDA speakers at the Public Meeting, the FDA should provide adequate training for field investigators in order to prevent the perception that the guidance document is a *de facto* regulation. The guidance document must continue to be developed with ample input from the PET community.

Background

Line 66 of the draft guidance document states that "an increasing number of PET centers are now operated by large, for-profit corporate entities that contract with academic and medical institutions…"

Comment

It is important for the FDA to understand that the commercial supply of PET radiopharmaceuticals remains a fledgling industry. We estimate that, while showing strong growth in recent years, the entire market for commercial PET producers remains small with a total market size of less than $70 million in

2001. In the same year, less than 200,000 patients received a PET radiopharmaceutical prepared at a commercial PET production facility. Although several companies may be considered commercial producers of PET radiopharmaceuticals, the aggregate profit margin of this industry remains slim due to falling dose prices.

What is a PET Drug?

Line 119 begins the section that describes PET drugs.

Comment

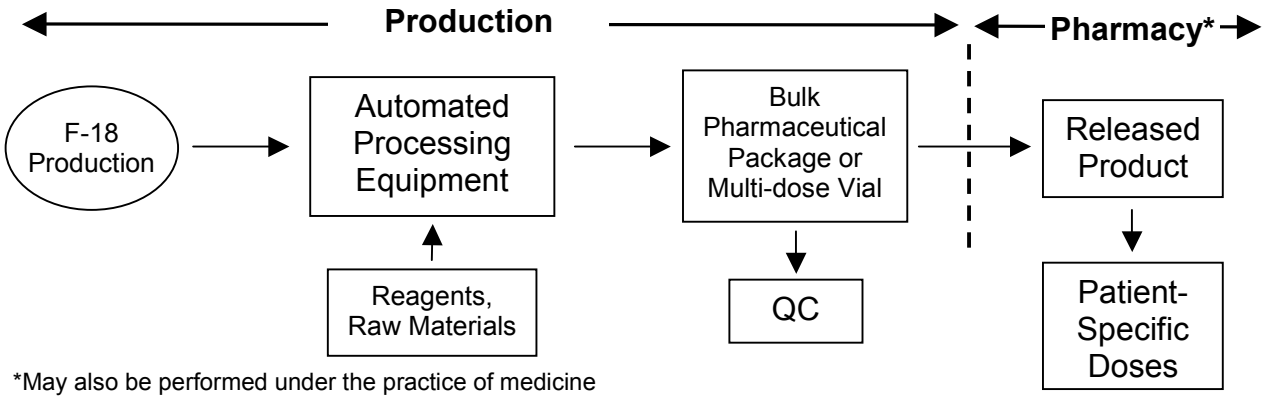
We believe the use of the term "drug" is inappropriate because it is inconsistent with the definition of an *in vivo* diagnostic radiopharmaceutical, which is described in 21 CFR 315. We suggest that, instead of the term "PET drug," the FDA adopt usage of the term "PET radiopharmaceutical."

Distinguishing Between PET Drug Production and the Practice of Pharmacy

Lines 155 through 177 describe how the FDA distinguishes between the production of PET radiopharmaceuticals and the practice of pharmacy.

Comment

We believe the most efficient handling of PET radiopharmaceuticals occurs when production operations coexist with the practice of pharmacy/medicine in the same facility or within very close proximity to each other. In fact, the final step of the production operation (filtration of the product into an empty sterile vial) may occur in the same hot cell that is used to dispense patient-specific doses. The vast majority of commercial PET radiopharmaceuticals will be produced in this hybrid environment. Therefore, it is critical that FDA regulation and PET CGMP's accommodate this environment, and that the FDA and the PET community develop a mutually agreeable understanding of where FDA regulation and the practice of pharmacy/medicine begin and end. To assist in this effort, we offer the following diagram:



*May also be performed under the practice of medicine

We suggest that the guidance document be modified to accurately reflect this environment, including the recognition that during the "distribution" of a PET radiopharmaceutical, the vial may not even leave the hot cell where it was produced.

Personnel Resources

Lines 209 through 216 of the draft guidance document discuss adequate personnel used in the production of PET radiopharmaceuticals, stating "For a PET center that typically produces a few doses daily of a PET drug for its own patients, it may be adequate to employ one or two persons to accomplish all production and quality control functions."

Comment

We believe that the complexity of a commercial PET production facility is best characterized by the number of *batches* produced each day, not by the number of doses. This is true regardless of the strength of the product in the batch (i.e., the production of a batch containing 10 mCi is equally complex

as the production of a batch containing 1000 mCi). This interpretation is also consistent with the fact that the number of doses is related to the practice of pharmacy. A simple commercial operation may be characterized by the production of one or two batches each day. It is adequate to employ one or two persons to accomplish all production and quality control functions in simple commercial operations. More complex commercial operations may be characterized by the production of three or more batches each day. It is adequate to employ two or more persons to accomplish all production and quality control functions in more complex commercial operations.

In addition, physician referral patterns for PET radiopharmaceuticals may be sporadic. It is possible that a facility may produce several batches of product on one day, and a single batch on another. In this situation, the same facility would be a complex operation on one day, and a simple operation on another. The regulatory framework must accommodate this possibility as well.

Quality Control

Lines 245 through 297 of the draft guidance document discuss quality control used in the production of PET radiopharmaceuticals.

Comment

We believe that the guidance document should clearly differentiate between the *oversight* of quality control functions and the *execution* of quality control functions. Quality control oversight may include:

- Assuring that PET radiopharmaceuticals have adequately defined identity, strength, quality and purity
- Approval and examination of specifications, methods, processes and procedures
- Assuring adequate investigation of errors, final product failures and final product complaints

It is possible to provide oversight with resources located outside the PET production facility. For example, facilities may use consultants to provide oversight, or may rely on a corporate QA/QC department. We believe that the "quality control unit" pertains only to the oversight of the quality control function. Regardless of the size or complexity of the commercial PET production facility, the oversight of the quality control function should be a separate organizational element from the production element.

The execution of quality control functions in a PET production facility must be the responsibility of personnel located at the facility. Some examples of these functions include:

- Acceptance/rejection of components, final product containers and labeling
- Acceptance/rejection of final PET radiopharmaceuticals
- Examination of specifications, methods, processes and procedures

Regardless of the size or complexity of the PET production facility, it should be possible for production personnel to execute quality functions.

A decision to reject batches based on the execution of the quality control function should not be subject to further review or revocation by another organizational unit or person. This model provides adequate control over production operations with a regulatory burden consistent with the current state of PET technology.

Facilities and Equipment

Lines 300 through 369 of the draft guidance document discuss quality control used in the production of PET radiopharmaceuticals.

Comments

Lines 330 and 331 discuss lead shielding. To our knowledge, there has never been a recognized danger of product contamination from lead shielding in the practice of nuclear pharmacy or medicine, and it is not obvious to us how such contamination could occur. We suggest that this sentence be removed.

Lines 351 through 369 discuss different facility requirements for small and large PET production facilities. Line 363 states "In large PET centers having relatively complex operations, separate and well-defined areas or rooms may be warranted for each independent function of the operation, such as production, testing, and storage of components." We believe that, regardless of size, areas within a PET production facility should be organized to prevent mix-ups. However, we know of no commercial PET production operation that is complex enough to warrant the use of different rooms for production, QC testing, and storage of components. We suggest the following changes. Eliminate the phrase "In small PET centers" from line 351. Replace lines 362 through 369 with "As the complexity in a PET production facility increases, it is important to develop the appropriate level of control required to prevent mix-ups and contamination. It is also important to consider what impact a greater number of personnel and activities could have on the aseptic processing portion of the process."

Aseptic Processing

Lines 371 through 420 of the draft guidance document discuss the aseptic processing area in the PET production facility.

Comments

Line 371 describes this section as "Aseptic Processing Facility." We suggest that this be changed to "Aseptic Processing Area" to reflect the fact that this area is located within, and not separate from, the PET production facility.

Line 373 states "The aseptic work area should be suitable for the preparation of a sterile PET drug product." This might imply that the preparation (e.g., the radiochemical synthesis) occurs in the aseptic work area. We suggest that this sentence be modified to: "The aseptic work area should be suitable for the assembly of the aseptic components required for the preparation of a sterile PET drug product."

Line 382 includes "(2) storage of the sterility samples…" Since sterility test samples are radioactive when they are first withdrawn from the final product vial, we suggest that this requirement be removed.

Lines 408 through 420 describe the room where the laminar air flow hood is located. During the Public Meeting, FDA panelists noted that while the controls described in lines 408-420 are important, the air quality of the room is not mandated at class 10,000. We support this position.

Lines 413 through 416 state "Surfaces of the walls, floors, and ceilings in the aseptic work areas should be easily sanitized and capable of withstanding frequent sanitizing. Cleaning and sanitizing should be performed frequently…" We suggest removal of the reference to sanitizing, and that this portion read: "Surfaces of the walls, floors, and ceilings in the aseptic work areas should be easily cleaned and should be cleaned frequently"

Gas Chromatograph

Lines 561 through 566 of the draft guidance document discuss the gas chromatograph (GC) used in a PET production facility. The draft guidance states "Appropriate system suitability testing procedures and criteria (see USP General Chapter <621> *Chromatography*) should help ensure the correct performance of the GC system."

Comment

The system suitability tests described in USP Chapter <621> include tests for resolution, replicate injections and tailing factor. Although we believe the GC system, including the analyst, must provide reproducible results, the test for replicate injections is not appropriate for the time critical environment of commercial PET production facilities because it requires an inordinate number of standard injections every day (5 or 6). Rather than a reference to USP Chapter <621>, we believe the draft guidance document should provide appropriate guidance for routine tests used to ensure proper performance of the instrument. The guidance should be consistent with the use of GC for tests that do not assay the active PET ingredient. The same observations apply to HPLC as discussed in lines 568 through 577.

Dose Calibrator

Line 581 of the draft guidance document discusses the dose calibrator used a PET production facility.

Comment

The phrase "that gives a printout" should be removed from line 581.

Control of Components, Containers and Closures

Line 636 of the draft guidance document begins the discussion of the control of components used in a PET production facility.

Comment

We believe the application of the nomenclature "components, containers and closures" to PET drug production inaccurately reflects the nature of PET production methodology. This nomenclature has its roots in pharmaceutical processes where a liquid drug product is added to an empty container, the container is sealed with a closure and the assembled unit subjected to further processing as necessary. This situation differs significantly from the preparation of commercial PET radiopharmaceuticals, where the product is aseptically transferred into a single, commercially-available, pre-assembled vial that is used as the container for the final drug product. We suggest removal of the phrase "container and closure" throughout the draft guidance document and use of the phrase "final product container" to describe the pre-assembled, empty vial.

Vendor Selection

Line 648 of the draft guidance document states "PET centers should obtain assurance from a vendor that the vendor will report any major changes in the manufacture of an item."

Comment

We believe that it will be impossible to implement this requirement. Commercial PET production facilities do not possess sufficient leverage with vendors to command such assurances. We believe that reliance on predetermined component specifications provides sufficient control for purposes of PET production facilities.

Receipt of Materials

Line 659 of the draft guidance document states "Sufficient information should be documented to enable the PET center to have full accountability and traceability of each lot."

Comment

Very small quantities of some reagents are used in the production of commercial PET radiopharmaceuticals. Consequently, it is difficult to maintain "a full accountability," or inventory of raw materials. During the Public Meeting, FDA panelists noted that accountability is not intended to mean inventory. We encourage the FDA to maintain this understanding and to modify "full accountability and traceability" to "full traceability."

Specific Identity Tests

Lines 711 to 755 of the draft guidance document discuss the use of specific identity tests for components that yield active PET ingredients or inactive ingredients.

Comment

We believe adequate control in the routine acceptance of components can be achieved without specific identity tests (e.g., mass spectrometry, infrared spectroscopy, or nuclear magnetic resonance spectrometry). In fact, we believe that the use of specific identity tests places a burden on commercial PET production facilities without added control in the quality of the raw material. Instead, we suggest the following controls for incoming components that yield an active PET ingredient:

a. Examination of a certificate of analysis[‡] for the incoming component and comparison to pre-determined specifications
b. When possible, performance of a non-specific identity test (e.g., an accurate melting point determination for mannose triflate)
c. 100% testing of the final product (i.e., [^{18}F]FDG from mannose triflate) prior to release.

Of course, the actual controls for incoming components should be described by the sponsor in a new drug application.

Production and Process Controls

Lines 808 and 895 of the draft guidance document refer to "dates of production steps."

Comment

We suggest that these lines be changed to "production date."

Master/Batch Production and Control Record

Line 817 of the draft guidance document begins the discussion of Master and Batch Production Records.

Comment

We request that the FDA consider the possibility that a Master Record provide a complete description of the PET production process, while the Batch Record provide only the information required for a documented history of the Batch in question. In this way, the Master Record, which may be 10 pages or more, is a descriptive tool and the Batch Record, which may be 3 pages or less, is a documentation tool. We believe this approach simultaneously offers appropriate controls for the commercial production of PET radiopharmaceuticals while minimizing large amounts of paperwork generated from the production of numerous daily batches.[†]

We suggest that line 878, which currently reads "Information in the batch record should be an accurate reproduction (paper, or electronic copy) of the master production record," be changed to "The information in the batch record (paper, or electronic copy) accurately reflects the information contained in the master production record."

Microbiological Control of Aseptic Processing and Sterilizing Filtration

Lines 995 through 998 of the draft guidance document discuss aseptic processing in the production of PET radiopharmaceuticals.

Comment

We believe that the only aseptic process pertinent to the production of a commercial PET radiopharmaceutical (e.g., [^{18}F]FDG) is the assembly of pre-sterilized components to form a

Lines 1013 through 1015 of the draft guidance document states "Before using filters from a particular lot, a sample should be tested for integrity to demonstrate that the membrane has the ability to retain microorganisms."

[‡]The COA should be signed by the supplier, and should include the results of specific identity tests.
[†]PETNet estimates that our current nationwide production output of MetaTrace FDG® is more than 60 batches/day. We are therefore very concerned about paperwork requirements associated with Master/Batch Production Records.

Comment

We believe that integrity tests assess the construction of the membrane filter housing and the integrity of the membrane, but cannot be used to demonstrate whether or not the membrane has the ability to retain microorganisms. We suggest that lines 1013 through 1015 be removed.

Test Record Requirements

Lines 1094 and 1105 of the draft guidance document describe required QC records for each batch of PET radiopharmaceutical.

Comment

We believe this section inaccurately reflects the relationship between the QC and production functions used in the preparation of PET radiopharmaceuticals. In the vast majority of cases, these areas are located within the same room, but this section implies otherwise.

We suggest that the following information is sufficient for the test records used for a PET radiopharmaceutical (e.g., by gas chromatography). A print-out of the chromatogram with the calculated amounts of each component analyzed by the test, the date the test was performed, the procedure used to perform the test, the batch identification number of the PET radiopharmaceutical, a statement of how the results compare with established acceptance criteria (i.e., pass/fail), and the initials of the analyst. This information may be directly recorded on, or attached to, the batch record.

Requirements for Laboratory Reference Standards

Lines 1126 through 1134 of the draft guidance document describe requirements for determination of identity and purity of reference standards used to test PET radiopharmaceuticals.

Comment

We believe this section describes inappropriate requirements for testing some unofficial standards that are used to test PET radiopharmaceuticals. Examples of unofficial standards used in the testing of [^{18}F]FDG include K222, acetonitrile and ethanol. We believe that the acceptance criteria for these standards should be no more stringent than the acceptance criteria for the same materials used in production. We suggest that the draft guidance document be modified to reflect this situation.

Microbiological Tests for Sterile PET Radiopharmaceuticals

Lines 1205 through 1208 of the draft guidance document describe requirements for Microbiological Tests for Sterile PET Radiopharmaceuticals.

Comment

Approved NDA #20-306 for [^{18}F]FDG provides for final product release prior to completion of the test for bacterial endotoxins. In this NDA, the 60-minute test for bacterial endotoxins must be started, but does not have to be complete, at the time of product release. Therefore, we suggest this section be changed to allow this provision. This provision is consistent with monograph for [^{18}F]FDG in the European Pharmacopeia, Third Edition, which states “The injection may be released for use before completion of the test [for bacterial endotoxin].” Finally this provision is consistent with Chapter 125, *Radiopharmaceutical Preparations* in the European Pharmacopeia, Third Edition, which states “It is sometimes difficult to carry out [bacterial endotoxin tests] before releasing the batch for use when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production.”

Accepting and Releasing a Batch

Line 1224 of the draft guidance document begins discussion of the accepting and release of a batch of PET radiopharmaceutical.

Comment

This section should be consistent with earlier comments regarding oversight and execution of the quality control function (see above).

Labeling and Packaging

Line 1287 of the draft guidance document begins discussion of labeling and packaging of PET radiopharmaceuticals.

Comment

This section should reflect the labeling methodology described in approved NDA #20-306 for [^{18}F]FDG. In this NDA, the empty final product vial is labeled with partial information (e.g., product name, batch number, preparation date, etc.) prior to filtration of the radioactive product. Then, after the radioactive assay has been performed, the outer shielded container and the Batch Record are labeled with all required information. We believe this section should be modified to include this labeling methodology.

Line 1303 of the draft guidance document states "For PET centers producing and distributing a large volume of PET drugs, the quality control unit should verify the contents of each label for accuracy and completeness."

Comment

This section should be consistent with earlier comments regarding oversight and execution of the quality control function, as well as the recognition of the fact that the number of doses is related to the practice of pharmacy.

Distribution

Line 1307 of the draft guidance document begins discussion of the distribution of PET radiopharmaceuticals.

Comment

As we discussed earlier in this letter, the vast majority of commercial PET radiopharmaceuticals will be produced in a hybrid environment where production operations coexist with the practice of pharmacy in the same facility or within very close proximity to each other. This section of the guidance document should be rewritten to recognize the fact that the receiving facility may be a pharmacy within the same facility as the production operation.

We believe that lines 1311 through 1314 contradict statements made earlier in the draft guidance document in lines 1234-1244. We request clarification on this point and suggest that lines 1311-1314 be modified to be consistent with earlier statements.

Lines 1320 through 1326 describe recall procedures, but recall procedures have appropriately been removed from the preliminary draft proposed rule. We request clarification on this point and suggest that references to recall be removed from the draft guidance document.

Sincerely,

Steve Zigler

Steve Zigler, Ph.D.
Director, Quality and Regulatory Affairs